



## · 专题论著 ·



王卓颖，主任医师，博士研究生导师，现任上海交通大学医学院附属仁济医院头颈外科主任。主要从事甲状腺、唾液腺、软组织及其他头颈部良恶性肿瘤的诊断和治疗的临床及研究工作。担任中国临床肿瘤学会甲状腺癌专家委员会副主任委员，中国抗癌协会头颈肿瘤专业委员会常委。曾获得中国抗癌协会科技奖二等奖、上海市抗癌协会科技奖三等奖、2020年黄浦区领军人才等。主持国家自然科学基金面上项目两项，承担上海市自然科学基金及上海市科技委员会引导项目等，引导上海交通大学医学院“青年科技创新工作室”，负责及参与多项国际及全国多中心临床研究，发表论文50余篇，其中多篇发表在SCI收录期刊上。主编或参与编写论著6部。主持建立了多中心的儿童及青少年甲状腺癌临床数据库，对Hippo通路介导Treg细胞分化发育在调控青少年甲状腺癌淋巴结转移中的作用机制开展了深入研究。目前，已在甲状腺领域权威期刊*Thyroid*上发表首篇国内儿童及青少年分化型甲状腺癌临床数据及测序分析报道。此外，团队还领导并顺利开展“选择理想的甲状腺乳头状微小癌患者密切随访研究”“*BRAF*、*TERT*和*RET/PTC*基因检测辅助甲状腺结节良恶性诊断的前瞻性及双盲非干预性临床试验”“甲磺酸阿帕替尼片新辅助治疗局部晚期分化型甲状腺癌患者的有效性和安全性研究”等数项国内多中心前瞻性临床研究，建立了甲状腺结节穿刺诊断的多基因联合检测体系，协助甲状腺癌的精准确诊，也为晚期甲状腺癌患者提供了新的药物治疗方案，延长了生存时间，提高了生活质量。

# 基因突变特征与儿童及青少年分化型甲状腺癌远处转移相关性的meta分析

邓姝婷，冯 源，钱 凯，郭 凯，王卓颖

上海交通大学医学院附属仁济医院头颈外科，上海 200001

〔摘要〕 背景与目的：甲状腺癌是世界范围内增长率较高的恶性肿瘤之一，在儿童及青少年中甲状腺癌的发病率也在逐年增加。本研究旨在对基因突变特征与儿童及青少年分化型甲状腺癌（differentiated thyroid carcinoma, DTC）远处转移的相关性进行meta分析。方法：数据库搜索探究基因突变特征与儿童及青少年DTC远处转移相关性的研究，运用STATA 14.0软件分析与远处转移相关的基因突变特征。结果：纳入20项研究，共涉及1 273例患者，分析结果显示，*BRAF* V600E突变阴性、*RET*基因融合阳性是儿童及青少年DTC远处转移的危险因素，而*NTRK*基因融合与远处转移未见明显相关性。结论：本研究发现了与儿童及青少年DTC远处转移相关的几个基因突变特征，有利于患者预后的评估及治疗方案的制定。

〔关键词〕 分化型甲状腺癌；儿童及青少年；远处转移；基因突变

DOI: 10.19401/j.cnki.1007-3639.2022.05.003

中图分类号：R736.1 文献标志码：A 文章编号：1007-3639(2022)05-0388-09

基金项目：国家自然科学基金（81972496，81772852）；上海市自然科学基金（16ZR1406600）；2020年度黄浦区领军人才计划；共青团上海交通大学医学院委员会“甲状腺肿瘤防治”青年科技创新工作室。

第一作者：邓姝婷（ORCID: 0000-0002-2894-5570），本科 E-mail: 517710910039@shsmu.edu.cn

通信作者：王卓颖（ORCID: 0000-0002-8121-5286），博士，主任医师，上海交通大学医学院附属仁济医院头颈外科主任

E-mail: zhuoyingwang@hotmail.com

**Meta-analysis of the association between gene alterations and distant metastasis of differentiated thyroid carcinoma in children and adolescents** DENG Shuting, FENG Yuan, QIAN Kai, GUO Kai, WANG Zhuoying (Department of Head and Neck Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200001, China)

Correspondence to: WANG Zhuoying E-mail: zhuoyingwang@hotmail.com

[ **Abstract** ] **Background and purpose:** Thyroid cancer is one of the fastest increasing malignancies worldwide, and its incidence in children and adolescents has also been increasing over the years. Meta-analysis were performed to investigate the correlation between gene alteration patterns and distant metastasis of differentiated thyroid carcinoma (DTC) in children and adolescents. **Methods:** Databases were used to search studies on the association between gene alteration patterns and distant metastasis of DTC in children and adolescents, and STATA 14.0 software was used to analyze the gene alterations related to distant metastasis. **Results:** Twenty studies involving 1 273 patients were included, and the analysis showed that negative BRAF V600E mutation and positive RET gene fusion were risk factors for distant metastasis in DTC in children and adolescents, while NTRK gene fusion was not significantly associated with distant metastasis. **Conclusion:** Our research identified several genetic alterations associated with distant metastasis in DTC in children and adolescents, which could be guidance for prognosis assessment and treatment planning.

[ **Key words** ] Differentiated thyroid cancer; Children and adolescents; Distant metastasis; Gene mutation

甲状腺癌是世界范围内增长率较高的恶性肿瘤之一<sup>[1]</sup>,在儿童及青少年中甲状腺癌的发病率也在逐年增加<sup>[2-3]</sup>。分化型甲状腺癌(differentiated thyroid carcinoma, DTC)是儿童及青少年甲状腺癌最常见的病理学类型,其中75%~90%为甲状腺乳头状癌(papillary thyroid cancer, PTC),其余大多为甲状腺滤泡癌(follicular thyroid cancer, FTC)<sup>[2]</sup>。

既往报道,儿童及青少年DTC患者与成人DTC患者在临床表现、病理学和分子特征等方面存在显著差异<sup>[4-6]</sup>。儿童及青少年DTC在疾病诊断时往往表现出进展程度高的特征,其中颈部淋巴结转移率为40%~90%,大致为成人的2倍,远处转移率为20%~30%,而成人仅为2%<sup>[7-8]</sup>。尽管儿童及青少年DTC出现肿瘤腺外侵犯、淋巴结转移及远处转移的概率较高,但儿童及青少年DTC预后仍较好,长期生存率超过90%。

部分研究者认为成人与儿童DTC在临床表现和预后上的差异可能是由于两者基因特征不同。在成人DTC中,较常见的基因改变是BRAF V600E突变、RAS突变及RET融合<sup>[9-10]</sup>;在儿童及青少年DTC中,RET融合、NTRK3融合和BRAF融合(AGK-BRAF、AKAP9-BRAF)的发生率较高,BRAF V600E突变较少见,RAS突变和TERT突变则更加罕见<sup>[11-15]</sup>。

目前对于儿童及青少年DTC远处转移相关的基因特征尚存争议。考虑到儿童及青少年DTC中远处转移人数较少,与基因特征相关的研究也仍未达成共识。因此本研究对基因突变特征与儿童及青少年DTC患者远处转移的相关性进行meta分析,探究儿童及青少年DTC中具有远处转移预测价值的分子生物标志物。

## 1 资料和方法

### 1.1 检索策略

2名研究者独立通过PubMed、Embase、Web of Science及CNKI数据库进行文献检索。检索时间为2012年1月—2022年2月,语言限制为中文或英文。英文数据库检索词主要有“thyroid cancer”“children”“adolescent”“mutation”“fusion”“BRAF”“RET”“NTRK”等,中文数据库检索词主要有“甲状腺癌”“分化型甲状腺癌”“儿童”“青少年”“遗传变异”“基因融合”“BRAF”“RET”“NTRK”等。为验证检索结果的完整性,研究者还手工查阅了相关论文的参考文献列表。

### 1.2 纳入与排除标准

#### 1.2.1 纳入标准

①研究对象为经组织病理学诊断为DTC(包

括PTC和FTC)的儿童及青少年患者(年龄 $\leq 24$ 岁);②研究类型为回顾性研究,内容包括患者远处转移及基因特征相关数据;③远处转移相关危险因素的比值比(odds ratio, OR)及95% CI可直接或通过原始数据计算获得。

### 1.2.2 排除标准

①远处转移总例数 $< 5$ ;②重复发表的文献;③文献类型为综述、信件、病例报道、会议摘要等;④原始数据不完整,不包含远处转移或基因事件相关数据。

### 1.3 数据提取

2名研究者独立对符合纳入标准的研究进行数据提取,如遇分歧则通过讨论或由第3人裁定。提取的数据包含作者姓名、发表年份、国家、研究时段、患者特征(年龄及性别)、远处转移人数及占比、手术方式、术后进行放射性碘(radioactive iodine, RAI)治疗比例、平均随访时长及各基因特征检测方法等,同时包含纳入对象的结局指标,包括与远处转移有关的*BRAF*、*RET*和*NTRK*等基因特征。

### 1.4 文献质量评估

2名评价员独立采用偏倚风险评估工具纽卡斯尔-渥太华评分表(Newcastle-Ottawa scale, NOS)对所纳入的病例对照研究进行文献质量评估,如遇分歧则通过讨论或由第3人裁定。评估内容主要包括研究人群选择方法(0~4分)、组间可比性(0~2分)及暴露因素测量(0~3分)。根据以上各个项目具体要求评分,用NOS总分值评估文献质量,其中 $> 7$ 分为高质量,6~7分为中等质量, $\leq 5$ 分为低质量,最终评价结果纳入文献基本信息表。

### 1.5 统计学处理

数据分析使用STATA 14.0软件,本研究以 $I^2$ 值来评估纳入研究文献的异质性,若 $I^2 \leq 50\%$ ,表明文献异质性不显著,采用固定效应模型进行数据合并;若 $I^2 > 50\%$ ,表明文献异质性显著,先进行敏感性分析找出异质性的来源,再对可能产生异质性的因素进行亚组分析,若各研究间无临床异质性时,采用随机效应模型进行数据合并。通过计算合并效应量的OR及95% CI来评估

结局指标,并对合并效应量进行Z检验, $P < 0.05$ 为差异有统计学意义。本研究采用漏斗图、Egger's法对文献发表偏倚进行评估,若 $P \geq 0.1$ 时则认为无明显发表偏倚,若 $P < 0.1$ ,则认为存在发表偏倚。

## 2 结 果

### 2.1 检索结果

根据检索策略,从PubMed、Embase、Web of Science及CNKI数据库中共检索出相关文献共3 247篇。剔除重复文献后,对剩余的2 293篇文献进行初步筛选。仔细阅读上述文献摘要和标题后,排除内容明显不相关的文献1 976篇以及综述、信件、病例报道、会议摘要等文献229篇,得到需要获取全文的文献共88篇。经过阅读全文,排除68篇不符合纳入标准的文献,最终纳入20篇文献进行meta分析。文献检索流程见图1,纳入文献基本信息见表1。

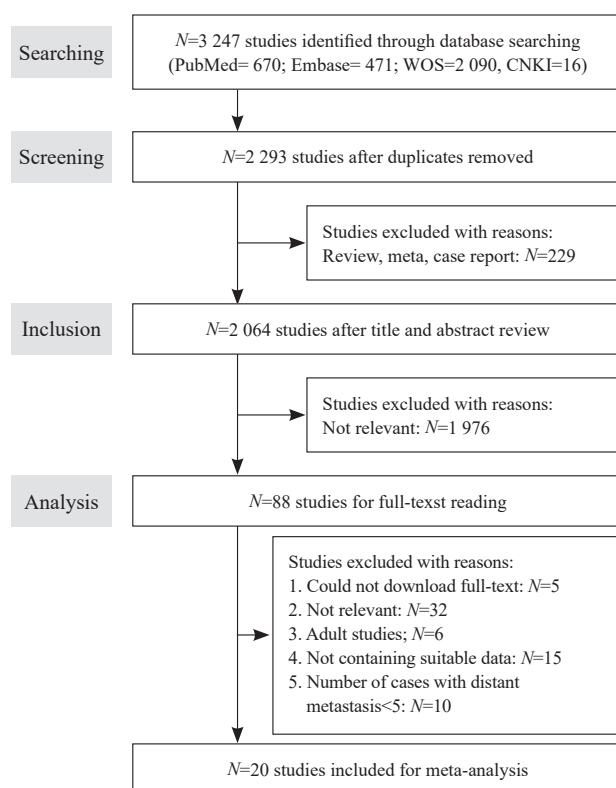


图1 Meta分析的文献筛选流程图

Fig. 1 Flow chart for literature search processing in the meta-analysis

表1 纳入文献基本信息

Tab. 1 Characteristics of included studies

| Author                     | Published year | Country | Study period | Definition /year | Mean age (range)  | Distant metastasis/total (%) | Surgical treatment (%) | RAI/% | Mean follow-up period t/year | Genetic events                                              | Detection method                       | NOS quality |
|----------------------------|----------------|---------|--------------|------------------|-------------------|------------------------------|------------------------|-------|------------------------------|-------------------------------------------------------------|----------------------------------------|-------------|
| Sui <sup>[16]</sup>        | 2019           | China   | 2005-2018    | ≤20              | 14.54±4.43        | 40/69 (57.8)                 | TT (100.0)             | 100   | 2.7                          | <i>BRAF</i>                                                 | NR                                     | M           |
| Zhao <sup>[17]</sup>       | 2020           | China   | 2007-2019    | ≤20              | NR                | 10/77 (13.0)                 | NR                     | NR    | NR                           | <i>BRAF</i>                                                 | DS                                     | M           |
| Geng <sup>[18]</sup>       | 2019           | China   | 2000-2015    | ≤14              | 7.05±1.65         | 6/39 (15.4)                  | NR                     | NR    | NR                           | <i>BRAF</i>                                                 | DS                                     | M           |
| Cordioli <sup>[15]</sup>   | 2016           | Brazil  | 1993-2012    | ≤18              | 11.36±4.52        | 10/30 (33.3)                 | TT (100.0)             | NR    | NR                           | <i>AGK-BRAF</i>                                             | RT-PCR                                 | M           |
| Sisdelli <sup>[13]</sup>   | 2019           | Brazil  | 1993-2017    | ≤18              | 12.64±4.08        | 24/80 (30.0)                 | TT (100.0)             | NR    | NR                           | <i>AGK-BRAF</i><br><i>BRAF</i>                              | RT-PCR, FISH<br>DS                     | M           |
| Chakraborty <sup>[6]</sup> | 2020           | India   | 2005-2018    | ≤20              | 17.00 (14.0-19.0) | 17/95 (17.9)                 | TT (83.2)<br>HT (16.8) | 33.7  | 2.5                          | <i>BRAF</i>                                                 | DS                                     | M           |
| Givens <sup>[19]</sup>     | 2014           | America | 1999-2012    | ≤18              | 13.55±3.33        | 5/19 (26.3)                  | TT (100.0)             | NR    | NR                           | <i>BRAF</i>                                                 | Pyrosequencing                         | H           |
| Geng <sup>[20]</sup>       | 2018           | China   | 1994-2014    | ≤18              | (3.6-13.8)        | 7/48 (14.6)                  | TT (56.3)<br>HT (43.7) | NR    | NR                           | <i>BRAF</i>                                                 | DS                                     | M           |
| Onder <sup>[21]</sup>      | 2016           | Turkey  | 1995-2015    | ≤18              | 14.74±3.36        | 5/50 (10.0)                  | TT (100.0)             | 76.0  | 5.8                          | <i>BRAF</i>                                                 | MASA-PCR                               | H           |
| Geng <sup>[57]</sup>       | 2019           | China   | NR           | ≤18              | NR                | 7/48 (14.6)                  | TT (56.3)<br>HT (43.7) | NR    | NR                           | <i>TERT</i>                                                 | DS                                     | L           |
| Stosic <sup>[22]</sup>     | 2021           | Canada  | NR           | ≤18              | 12.80±2.90        | 11/52 (21.2)                 | NR                     | NR    | NR                           | <i>BRAF</i><br><i>RET</i>                                   | MASA-PCR<br>q-PCR                      | H           |
| Franco <sup>[23]</sup>     | 2022           | America | 1989-2019    | ≤18              | 14.53±2.99        | 22/131 (16.8)                | TT (100.0)             | 65.6  | NR                           | <i>RET</i><br><i>NTRK</i><br><i>BRAF</i><br><i>RAS</i>      | NGS                                    | M           |
| Cordioli <sup>[12]</sup>   | 2017           | Brazil  | NR           | ≤18              | 11.80±4.48        | 13/35 (37.1)                 | TT (100.0)             | NR    | NR                           | <i>BRAF</i><br><i>NTRK</i><br><i>AGK-BRAF</i><br><i>RET</i> | DS<br>RT-PCR<br>RT-PCR, FISH<br>RT-PCR | H           |
| Alzahrani <sup>[24]</sup>  | 2020           | Saudi   | 2004-2019    | ≤18              | 17.00 (5.0-18.0)  | 5/48(10.4)                   | TT (100.0)             | 89.6  | 10.8                         | <i>BRAF</i><br><i>RET</i>                                   | NGS                                    | M           |
| Potter <sup>[25]</sup>     | 2021           | America | 2005-2016    | ≤24              | NR                | 10/36 (27.8)                 | NR                     | 94.0  | NR                           | <i>BRAF</i><br><i>RET</i><br><i>NTRK</i>                    | NGS                                    | M           |
| Lee <sup>[26]</sup>        | 2021           | Korea   | 1983-2020    | ≤20              | 14.30±3.80        | 20/106 (18.9)                | NR                     | NR    | 7.3                          | <i>RET</i><br><i>NTRK</i><br><i>ALK</i><br><i>BRAF</i>      | Various methods                        | M           |
| Pekova <sup>[27]</sup>     | 2020           | Czech   | 2003-2019    | ≤20              | 14.50±3.40        | 10/93 (10.8)                 | TT (88.2)<br>ST (11.8) | 90.3  | 6.0                          | <i>RET</i><br><i>NTRK</i><br><i>ALK</i><br><i>BRAF</i>      | NGS,RT-PCR                             | M           |
| Alzahrani <sup>[28]</sup>  | 2017           | Saudi   | 1998-2015    | ≤18              | 15.50 (8.0-18.0)  | 9/79 (11.4)                  | TT (100.0)             | 92.4  | 5.4                          | <i>BRAF</i>                                                 | DS                                     | M           |
| Pekova <sup>[29]</sup>     | 2019           | Czech   | 2003-2017    | ≤20              | 14.2±3.4          | 10/83 (12.0)                 | TT (86.7)<br>HT (13.3) | 86.7  | 6.0                          | <i>RET</i><br><i>BRAF</i>                                   | RT-PCR<br>NGS                          | H           |
| Alzahrani <sup>[30]</sup>  | 2016           | Saudi   | NR           | ≤18              | 16.00 (9.0-18.0)  | 8/55 (14.5)                  | TT (100.0)             | 89    | NR                           | <i>BRAF</i>                                                 | DS                                     | M           |

NR: Not reported. TT: Total thyroidectomy. ST: Subtotal thyroidectomy. HT: Hemithyroidectomy. DS: Direct sequencing. RT-PCR: Reverse transcription-polymerase chain reaction. FISH: Fluorescence *in situ* hybridization. MASA-PCR: Mutant allele specific amplification-PCR. qPCR: Quantitative PCR. NGS: next generation sequencing.

## 2.2 儿童及青少年DTC患者远处转移与基因特征的关系

### 2.2.1 *BRAF* V600E突变

在18篇包含*BRAF* V600E突变的相关文献<sup>[6, 12-13, 16-30]</sup>中, Alzahrani等的研究共3篇, Pekova等的研究共2篇, 耿江桥等的研究共2篇, 考虑到上述文献的研究人群可能重合, 影响最终统计结果, 因此保留总样本量更大的文献纳入meta分析。最终纳入14篇包含*BRAF* V600E突变的相关文献<sup>[6, 12-13, 16-17, 19-23, 25-28]</sup>, 共计889例儿童及青少年DTC患者。*BRAF* V600E突变组共252例, 其中19例(7.5%)患者有远处转移; 无*BRAF* V600E突变组共637例, 其中171例(26.8%)患者有远处转移。异质性检验结果提示各研究间异质性不显著( $I^2=0.0\%$ ,  $P=0.462$ ), 采用固定效应模型计算*BRAF* V600E突变的合并效应量, 结果显示差异有统计学意义(OR=0.22, 95% CI: 0.13~0.38,  $P<0.000\ 01$ , 图2), 提示有*BRAF* V600E突变的儿童及青少年PTC患者远处转移的风险低于无*BRAF* V600E突变患者, 无*BRAF* V600E突变是儿童及青少年DTC患者远处转移的危险因素。

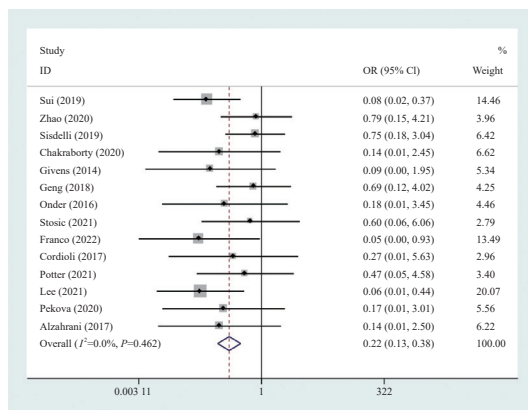


图2 *BRAF* V600E突变与儿童及青少年DTC患者远处转移关系的森林图

Fig. 2 Forest plot concerning the association of *BRAF* V600E mutation with distant metastasis in DTC in children and adolescents

### 2.2.2 *RET*基因融合

共8篇文献包含*RET*基因融合相关数据, 其中Pekova等<sup>[27, 29]</sup>的两项研究可能存在患者人群重合, 因此选择患者总人数更多的一篇文献纳入

meta分析。最终纳入7篇包含*RET*基因融合的相关文献<sup>[12, 22-27]</sup>, 共计444例儿童及青少年DTC患者。*RET*基因融合组共119例, 其中43例患者有远处转移(36.1%); 无*RET*基因融合组共325例, 其中46例患者有远处转移(14.2%)。异质性检验结果提示各研究间异质性较低( $I^2=38.3\%$ ,  $P=0.137$ ), 采用固定效应模型计算*RET*基因融合的合并效应量, 结果显示差异有统计学意义(OR=3.55, 95% CI: 2.16~5.85,  $P<0.000\ 01$ , 图3), 表明有*RET*基因融合的儿童及青少年PTC患者远处转移的风险是无*RET*基因融合的3.55倍, 因此*RET*基因融合是儿童及青少年DTC患者远处转移的危险因素。

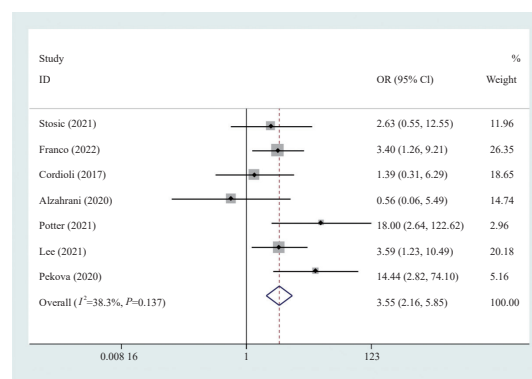


图3 *RET*基因融合与儿童及青少年DTC患者远处转移关系的森林图

Fig. 3 Forest plot concerning the association of *RET* gene fusion with distant metastasis in DTC in children and adolescents

### 2.2.3 *NTRK*基因融合

本文共纳入6篇包含*NTRK*基因融合的相关文献<sup>[12, 22-27]</sup>, 共计405例儿童及青少年DTC患者。*NTRK*基因融合组共41例, 其中9例患者有远处转移(22.0%); 无*NTRK*基因融合组共364例, 其中69例患者有远处转移(19.0%)。异质性检验结果提示各研究间异质性相对较低( $I^2=50\%$ ,  $P=0.075$ ), 采用固定效应模型计算*NTRK*基因融合的合并效应量, 结果显示差异无统计学意义(OR=1.48, 95% CI: 0.69~3.20,  $P=0.313$ , 图4), 表明*NTRK*基因融合与儿童及青少年DTC患者的远处转移无明显相关性。对上述*NTRK*基因融合相关文献绘制漏斗图(图5), 并进行

Egger's法检验, 结果提示可能存在发表偏倚。

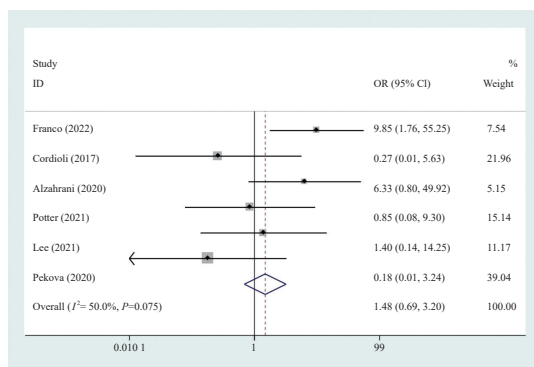


图4 *NTRK*基因融合与儿童及青少年DTC患者远处转移关系的森林图

Fig. 4 Forest plot concerning the association of *NTRK* gene fusion with distant metastasis in DTC in children and adolescents

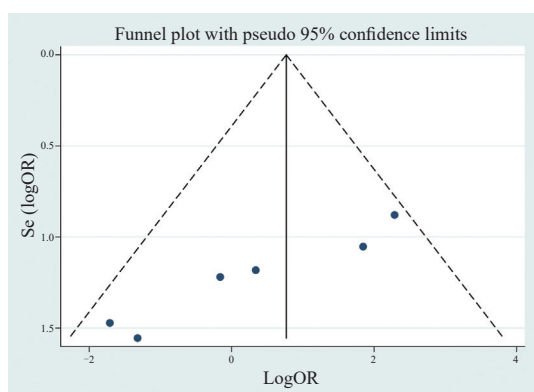


图5 *NTRK*基因融合与儿童及青少年DTC患者远处转移关系的漏斗图

Fig. 5 Funnel plot for assessing publication bias of the association between *NTRK* gene fusion and distant metastasis in DTC in children and adolescents

### 3 讨论

远处转移是影响DTC患者预后的重要因素。有研究<sup>[4-5]</sup>表明, 儿童及青少年DTC与成人DTC患者在临床表现和预后上有很大的差异。相较于成人, 儿童及青少年DTC患者在诊断时病灶往往表现出高侵袭性<sup>[31-33]</sup>, 除此之外, 儿童及青少年DTC患者远处转移率更高<sup>[34-35]</sup>。既往研究<sup>[36-37]</sup>证实, 肿瘤大小、多灶性、腺外侵犯及淋巴结转移等是儿童及青少年DTC患者远处转移的危险因素。随着近年来甲状腺癌基因检测技术的发展,

探究基因突变特征与儿童及青少年DTC患者疾病进展的关系有利于指导治疗, 改善患者预后。目前有关儿童及青少年DTC患者的基因特征与远处转移关系的研究仍较少, 且受到研究对象、研究设计及样本量等诸多因素的影响, 各研究结论不尽一致, 因此有必要进行meta分析定量研究, 确定与儿童及青少年DTC患者远处转移高风险有关的基因特征。

*BRAF*基因与丝裂原激活蛋白激酶 (mitogen-activation protein kinase, MAPK) 通路相关, 影响与细胞增殖、癌症进展相关的基因转录、调控及表达<sup>[38-39]</sup>。*BRAF* V600E突变是成人DTC患者中最常见的突变<sup>[40]</sup>, 研究<sup>[41-43]</sup>表明, *BRAF* V600E突变的成人DTC患者肿瘤恶性侵袭程度更高。然而, *BRAF* V600E突变在儿童及青少年DTC患者中并不常见<sup>[44-48]</sup>, 其中两项儿童研究<sup>[46, 49]</sup>评估了*BRAF* V600E突变与肿瘤侵袭性行为之间的关系, 并未发现显著相关性。在Givens等<sup>[19]</sup>的研究中, *BRAF* V600E突变的儿童及青少年DTC患者远处转移率更低。本研究的meta分析结果提示无*BRAF* V600E突变是儿童及青少年DTC患者远处转移的危险因素, 与上述文献结论一致。

*RET*基因与MAPK和磷脂酰肌醇3激酶 (phosphoinositide 3-kinase, PI3K) 通路相关, 该基因的激活可以促进癌细胞的生长、分化、增殖和存活<sup>[50-51]</sup>。相较于成人DTC患者, *RET*基因融合在儿童及青少年DTC患者中发生率较高 (24.6%~37.0%)<sup>[12,52]</sup>。*RET*基因融合是儿童及青少年DTC患者中最常见的一种基因融合, 在Pekova等<sup>[27]</sup>的研究中, *RET*基因融合的发生率为28%, 提示*RET*基因融合是儿童及青少年DTC患者远处转移的危险因素。而本文的meta分析结果提示儿童及青少年DTC患者中有*RET*基因融合的远处转移风险是无*RET*基因融合的3.55倍, 对于患者的预后有一定的预测价值, 提示未来通过对*RET*基因融合的检测, 有可能对远处转移风险进行预测, 从而进一步指导治疗, 提高远期生存率。

*NTRK*基因融合编码的融合蛋白会异常激活TRK激酶及下游通路<sup>[53]</sup>, 而该融合在

儿童及青少年DTC患者中的发生率为13.6%~26.0%<sup>[27, 54-56]</sup>。在Ricarte-Filho等<sup>[55]</sup>的研究中,*NTRK*基因融合阳性的儿童及青少年DTC患者表现出高远处转移率(9/20, 45%),而Pekova等<sup>[27]</sup>的研究却未得出类似结论。本文关于*NTRK*基因融合的meta分析结果显示差异无统计学意义,表明*NTRK*基因融合与儿童及青少年DTC患者远处转移无明显相关性。*NTRK*基因融合对儿童及青少年DTC患者预后的影响尚无定论,需要更大样本量的研究来验证。

本文探讨了与儿童及青少年DTC患者远处转移相关的基因特征,评估了*BRAF*、*RET*及*NTRK*等基因改变与远处转移的关系。本研究可以帮助临床医师根据基因检测结果来评估儿童及青少年DTC患者的预后并选择合适的治疗方案。本研究仍存在一定局限性。首先,大多数纳入的研究是回顾性研究,且未进行严格的混杂因素匹配,无法避免选择偏倚。其次,儿童及青少年DTC患者基因特征的相关研究数量还较少,文献样本量普遍较小,可能导致统计结果的偏倚,仍需要扩大样本量来减少误差产生。

综上所述,本研究确定了*BRAF* V600E突变阴性、*RET*基因融合阳性是儿童及青少年DTC患者远处转移的危险因素,而*NTRK*基因融合与远处转移未见明显相关性。通过对上述基因的检测,有利于儿童及青少年DTC患者预后评估及治疗方案制定。对具有上述危险因素的患者,采取个体化治疗的同时,应密切随访观察,以期对于远处转移早发现、早治疗,提高患者生存质量。

**利益冲突声明:** 所有作者均声明不存在利益冲突。

## [参 考 文 献]

- [1] SIEGEL R L, MILLER K D, FUCHS H E, et al. Cancer statistics, 2021 [J]. CA A Cancer J Clin, 2021, 71(1): 7-33.
- [2] HOGAN A R, YING Z G, PEREZ E A, et al. Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients [J]. J Surg Res, 2009, 156(1): 167-172.
- [3] VERGAMINI L B, FRAZIER A L, ABRANTES F L, et al. Increase in the incidence of differentiated thyroid carcinoma in children, adolescents, and young adults: a population-based study [J]. J Pediatr, 2014, 164(6): 1481-1485.
- [4] JARZAB B, HANDKIEWICZ-JUNAK D. Differentiated thyroid cancer in children and adults: same or distinct disease? [J]. Hormones (Athens), 2007, 6(3): 200-209.
- [5] ZIMMERMAN D, HAY I D, GOUGH I R, et al. Papillary thyroid carcinoma in children and adults: long-term follow-up of 1 039 patients conservatively treated at one institution during three decades [J]. Surgery, 1988, 104(6): 1157-1166.
- [6] CHAKRABORTY D, SHAKYA S, BALLAL S, et al. *BRAF* V600E and *TERT* promoter mutations in paediatric and young adult papillary thyroid cancer and clinicopathological correlation [J]. J Pediatr Endocrinol Metab, 2020, 33(11): 1465-1474.
- [7] NEIVA F, MESQUITA J, PACO LIMA S, et al. Thyroid carcinoma in children and adolescents: a retrospective review [J]. Endocrinol Y Nutr, 2012, 59(2): 105-108.
- [8] RIVKEES S A, MAZZAFERRI E L, VERBURG F A, et al. The treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy [J]. Endocr Rev, 2011, 32(6): 798-826.
- [9] XING M Z. Molecular pathogenesis and mechanisms of thyroid cancer [J]. Nat Rev Cancer, 2013, 13(3): 184-199.
- [10] AGRAWAL N, AKBANI R, AKSOY B A, et al. Integrated genomic characterization of papillary thyroid carcinoma [J]. Cell, 2014, 159(3): 676-690.
- [11] RICARTE-FILHO J C, LI S, GARCIA-RENDUELES M E R, et al. Identification of kinase fusion oncogenes in post-chemobyl radiation-induced thyroid cancers [J]. J Clin Invest, 2013, 123(11): 4935-4944.
- [12] CORDIOLI M I, MORAES L, BASTOS A U, et al. Fusion oncogenes are the main genetic events found in sporadic papillary thyroid carcinomas from children [J]. Thyroid, 2017, 27(2): 182-188.
- [13] SISDELLI L, CORDIOLI M I C V, VAISMAN F, et al. *AGK-BRAF* is associated with distant metastasis and younger age in pediatric papillary thyroid carcinoma [J]. Pediatr Blood Cancer, 2019, 66(7): e27707.
- [14] CIAMPI R, KNAUF J A, KERLER R, et al. Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer [J]. J Clin Invest, 2005, 115(1): 94-101.
- [15] CORDIOLI M I C V, MORAES L, CARVALHEIRA G, et al. *AGK-BRAF* gene fusion is a recurrent event in sporadic pediatric thyroid carcinoma [J]. Cancer Med, 2016, 5(7): 1535-1541.
- [16] 眭慧敏, 刘杰蕊, 王 瞳, 等. 儿童及青少年分化型甲状腺癌远处转移的临床病理学危险因素分析 [J]. 中国癌症杂志, 2019, 29(6): 423-428.
- [17] SUI H M, LIU J R, WANG T, et al. Clinicopathological risk factors for distant metastasis of differentiated thyroid carcinoma in children and adolescents [J]. China Oncol, 2019, 29(6): 423-428.
- [17] ZHAO J, HUANG M, LING R, et al. Clinicopathological features, *BRAF* V600E mutation rate and its clinical correlation for thyroid carcinoma in children and adolescent [J]. Modern

- Oncology, 2020, 28(07): 1120–1124.
- [ 18 ] 耿江桥, 王生才, 郭永丽, 等. 儿童甲状腺乳头状癌*BRAF*基因突变及其临床意义 [ J ] . 解放军医药杂志, 2019, 31(3): 47–49.
- GENG J Q, WANG S C, GUO Y L, et al. *BRAF* gene mutation and its clinical significance in children with thyroid papillary carcinoma [ J ] . Med Pharm J Chin People's Liberation Army, 2019, 31(3): 47–49.
- [ 19 ] GIVENS D J, BUCHMANN L O, AGARWAL A M, et al. *BRAF* V600E does not predict aggressive features of pediatric papillary thyroid carcinoma [ J ] . Laryngoscope, 2014, 124(9): E389–E393.
- [ 20 ] GENG J Q, WANG H M, LIU Y H, et al. Correlation between *BRAF* V600E mutation and clinicopathological features in pediatric papillary thyroid carcinoma [ J ] . Sci China Life Sci, 2017, 60(7): 729–738.
- [ 21 ] ONDER S, OZTURK SARI S, YEGEN G, et al. Classic architecture with multicentricity and local recurrence, and absence of *TERT* promoter mutations are correlates of *BRAF* (V600E) harboring pediatric papillary thyroid carcinomas [ J ] . Endocr Pathol, 2016, 27(2): 153–161.
- [ 22 ] STOSIC A, FULIGNI F, ANDERSON N D, et al. Diverse oncogenic fusions and distinct gene expression patterns define the genomic landscape of pediatric papillary thyroid carcinoma [ J ] . Cancer Res, 2021, 81(22): 5625–5637.
- [ 23 ] FRANCO A T, RICARTE-FILHO J C, ISAZA A, et al. Fusion oncogenes are associated with increased metastatic capacity and persistent disease in pediatric thyroid cancers [ J ] . J Clin Oncol, 2022, 40(10): 1081–1090.
- [ 24 ] ALZHRANI A S, ALSWAILEM M, ALSWAILEM A A, et al. Genetic alterations in pediatric thyroid cancer using a comprehensive childhood cancer gene panel [ J ] . J Clin Endocrinol Metab, 2020, 105(10): dgaa389.
- [ 25 ] POTTER S L, REUTHER J, CHANDRAMOHAN R, et al. Integrated DNA and RNA sequencing reveals targetable alterations in metastatic pediatric papillary thyroid carcinoma [ J ] . Pediatr Blood Cancer, 2021, 68(1): e28741.
- [ 26 ] LEE Y A, LEE H, IM S W, et al. *NTRK* and *RET* fusion-directed therapy in pediatric thyroid cancer yields a tumor response and radioiodine uptake [ J ] . J Clin Invest, 2021, 131(18): e144847.
- [ 27 ] PEKOVA B, SYKOROVA V, DVORAKOVA S, et al. *RET*, *NTRK*, *ALK*, *BRAF* and *MET* fusions in a large cohort of pediatric papillary thyroid carcinomas [ J ] . Thyroid, 2020, 30(12): 1771–1780.
- [ 28 ] ALZHRANI A S, MURUGAN A K, QASEM E, et al. Single point mutations in pediatric differentiated thyroid cancer [ J ] . Thyroid, 2017, 27(2): 189–196.
- [ 29 ] PEKOVA B, DVORAKOVA S, SYKOROVA V, et al. Somatic genetic alterations in a large cohort of pediatric thyroid nodules [ J ] . Endocr Connect, 2019, 8(6): 796–805.
- [ 30 ] ALZHRANI A S, QASEM E, MURUGAN A K, et al. Uncommon *TERT* promoter mutations in pediatric thyroid cancer [ J ] . Thyroid, 2016, 26(2): 235–241.
- [ 31 ] DINAUER C A, BREUER C, RIVKEES S A. Differentiated thyroid cancer in children: diagnosis and management [ J ] . Curr Opin Oncol, 2008, 20(1): 59–65.
- [ 32 ] GRIGSBY P W, GAL-OR A, MICHALSKI J M, et al. Childhood and adolescent thyroid carcinoma [ J ] . Cancer, 2002, 95(4): 724–729.
- [ 33 ] WELCH DINAUER C A, TUTTLE R M, ROBIE D K, et al. Clinical features associated with metastasis and recurrence of differentiated thyroid cancer in children, adolescents and young adults [ J ] . Clin Endocrinol, 1998, 49(5): 619–628.
- [ 34 ] CORDIOLI M I, MORAES L, CURY A N, et al. Are we really at the dawn of understanding sporadic pediatric thyroid carcinoma? [ J ] . Endocr Relat Cancer, 2015, 22(6): R311–R324.
- [ 35 ] ALZHRANI A S, ALKHAFI D, TULI M, et al. Comparison of differentiated thyroid cancer in children and adolescents ( $\leq 20$  years) with young adults [ J ] . Clin Endocrinol, 2016, 84(4): 571–577.
- [ 36 ] LIU Z M, HU D, HUANG Y H, et al. Factors associated with distant metastasis in pediatric thyroid cancer: evaluation of the SEER database [ J ] . Endocr Connect, 2019, 8(2): 78–85.
- [ 37 ] ZENG X, WANG Z H, GUI Z Q, et al. High incidence of distant metastasis is associated with histopathological subtype of pediatric papillary thyroid cancer—a retrospective analysis based on SEER [ J ] . Front Endocrinol (Lausanne), 2021, 12: 760901.
- [ 38 ] NUCERA C, LAWLER J, PARANGI S. *BRAF* (V600E) and microenvironment in thyroid cancer: a functional link to drive cancer progression [ J ] . Cancer Res, 2011, 71(7): 2417–2422.
- [ 39 ] VASKO V, ESPINOSA A V, SCOUTEN W, et al. Gene expression and functional evidence of epithelial-to-mesenchymal transition in papillary thyroid carcinoma invasion [ J ] . PNAS, 2007, 104(8): 2803–2808.
- [ 40 ] NUCERA C, GOLDFARB M, HODIN R, et al. Role of *B-Raf* (V600E) in differentiated thyroid cancer and preclinical validation of compounds against *B-Raf* (V600E) [ J ] . Biochim Biophys Acta, 2009, 1795(2): 152–161.
- [ 41 ] KIM S J, LEE K E, MYONG J P, et al. *BRAF* V600E mutation is associated with tumor aggressiveness in papillary thyroid cancer [ J ] . World J Surg, 2012, 36(2): 310–317.
- [ 42 ] TAKACSOVA E, KRALIK R, WACZULIKOVA I, et al. A different prognostic value of *BRAF* V600E mutation positivity in various age groups of patients with papillary thyroid cancer [ J ] . Neoplasma, 2017, 64(1): 156–164.
- [ 43 ] CZARNIECKA A, OCZKO-WOJCIECHOWSKA M, BARCZYŃSKI M. *BRAF* V600E mutation in prognostication of papillary thyroid cancer (PTC) recurrence [ J ] . Gland Surg, 2016, 5(5): 495–505.
- [ 44 ] TUFANO R P, TEIXEIRA G V, BISHOP J, et al. *BRAF* mutation in papillary thyroid cancer and its value in tailoring initial treatment [ J ] . Medicine, 2012, 91(5): 274–286.

- [ 45 ] NIKIFOROVA M N, CIAMPI R, SALVATORE G, et al. Low prevalence of *BRAF* mutations in radiation-induced thyroid tumors in contrast to sporadic papillary carcinomas [ J ] . Cancer Lett, 2004, 209(1): 1–6.
- [ 46 ] KUMAGAI A, NAMBA H, SAENKO V A, et al. Low frequency of *BRAF* T1796A mutations in childhood thyroid carcinomas [ J ] . J Clin Endocrinol Metab, 2004, 89(9): 4280–4284.
- [ 47 ] PENKO K, LIVEZEY J, FENTON C, et al. *BRAF* mutations are uncommon in papillary thyroid cancer of young patients [ J ] . Thyroid, 2005, 15(4): 320–325.
- [ 48 ] ROSENBAUM E, HOSLER G, ZAHURAK M, et al. Mutational activation of *BRAF* is not a major event in sporadic childhood papillary thyroid carcinoma [ J ] . Mod Pathol, 2005, 18(7): 898–902.
- [ 49 ] SASSOLAS G, HAFDI-NEJJARI Z, FERRARO A, et al. Oncogenic alterations in papillary thyroid cancers of young patients [ J ] . Thyroid, 2012, 22(1): 17–26.
- [ 50 ] SANTORO M, CARLOMAGNO F. Central role of *RET* in thyroid cancer [ J ] . Cold Spring Harb Perspect Biol, 2013, 5(12): a009233.
- [ 51 ] KUROKAWA K, KAWAI K, HASHIMOTO M, et al. Cell signalling and gene expression mediated by *RET* tyrosine kinase [ J ] . J Intern Med, 2003, 253(6): 627–633.
- [ 52 ] GALUPPINI F, VIANELLO F, CENSI S, et al. Differentiated thyroid carcinoma in pediatric age: genetic and clinical scenario [ J ] . Front Endocrinol (Lausanne), 2019, 10: 552.
- [ 53 ] WONG D, YIP S, SORESENSEN P H. Methods for identifying patients with tropomyosin receptor kinase (*TRK*) fusion cancer [ J ] . Pathol Oncol Res, 2020, 26(3): 1385–1399.
- [ 54 ] PRASAD M L, VYAS M, HORNE M J, et al. *NTRK* fusion oncogenes in pediatric papillary thyroid carcinoma in northeast United States [ J ] . Cancer, 2016, 122(7): 1097–1107.
- [ 55 ] RICARTE-FILHO J C, HALADA S, O'NEILL A, et al. The clinical aspect of *NTRK*-fusions in pediatric papillary thyroid cancer [ J ] . Cancer Genet, 2022, 262/263: 57–63.
- [ 56 ] ZHAO X N, KOTCH C, FOX E, et al. *NTRK* fusions identified in pediatric tumors: the frequency, fusion partners, and clinical outcome [ J ] . JCO Precis Oncol, 2021, 1: PO.20.00250.
- [ 57 ] GENG J Q, LIU Y H, GUO Y L, et al. Correlation between *TERT* C228T and clinic-pathological features in pediatric papillary thyroid carcinoma [ J ] . Sci China Life Sci, 2019, 62(12): 1563–1571.

( 收稿日期: 2022-03-25 修回日期: 2022-05-01 )

## 《中国抗癌协会乳腺癌诊治指南与规范（2021版）》 2022年指南主席团巡讲活动

《中国抗癌协会乳腺癌诊治指南与规范（2021版）》2022年度全国巡讲活动已展开，《中国抗癌协会乳腺癌诊治指南与规范（2021版）》结合乳腺癌治疗领域最新研究进展以及国内专家同道临床实践经验以更明确的观点、更精炼的文字、更清晰的图表、更缜密的逻辑，全方位展现乳腺癌的诊疗理念。

2022年度巡讲围绕“防治一体、分型而治、求同存异的原则，由业界知名专家携手国内乳腺专科医师、乳腺癌临床诊疗医师，共同解读指南精要内容，探讨科研热点话题通过临床案例的示教以期让广大乳腺癌诊疗医师、康复与随访专业人员满载而归！

巡讲议程请关注SIBCS官方微信，了解最新指南巡讲内容及学术动态：



《中国癌症杂志》编辑部